Neurophysiology of Lower Urinary Tract Function and Dysfunction

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With the continued aging of the population, the incidence of conditions associated with bladder control will continue to grow. In this article, we review the neurophysiology and pathophysiology of the bladder and urethra and discuss logical concepts for the development of novel drug therapy that can better help the expanding population of patients with bladder control problems.
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Key words: Overactive bladder • Capsaicin • Serotonin • Oxybutynin • Muscarinic receptors

Micturition can be visualized as a process in which neural circuits in the brain and spinal cord coordinate the activity of smooth muscle in the bladder and urethra.[1,2] These circuits act as on-off switches to alternate the lower urinary tract between 2 modes of operation: storage and elimination. Injuries or diseases of the nervous system in adults can disrupt the voluntary control of micturition and cause the reemergence of reflex micturition, resulting in bladder hyperactivity and urge incontinence.[3] Because central nervous control of the lower urinary tract is complex, urge incontinence can result from a variety of

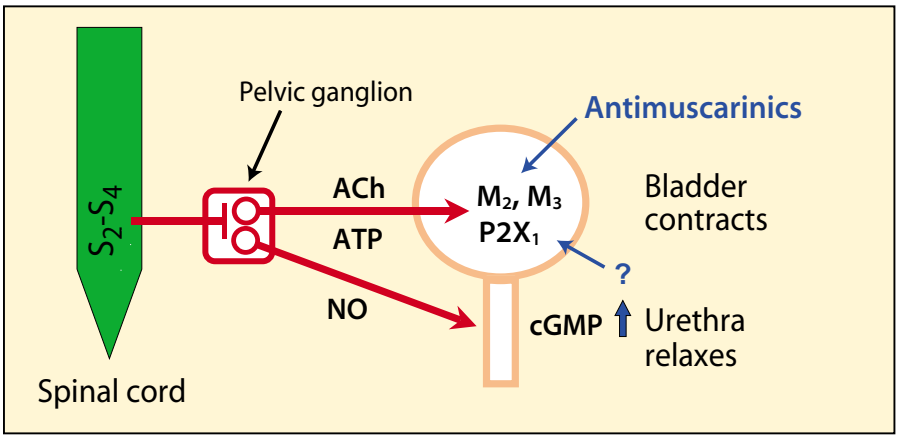


Figure 1. *Parasympathetic (pudendal nerve): Parasympathetic postganglionic nerve terminals release acetylcholine (ACh), which can excite various muscarinic receptors in bladder smooth muscles, leading to bladder contractions. ATP, adenosine triphosphate; NO, nitric oxide; cGMP, cyclic guanosine monophosphate.*

neurologic disorders and abnormal sensory activation. In addition, urge incontinence may be caused by intrinsic detrusor myogenic abnormalities that result in motor detrusor instability.[4]

Neural Control of the Lower Urinary Tract

The lower urinary tract is innervated by 3 sets of peripheral nerves involving the parasympathetic, sympathetic, and somatic nervous systems:

- Pelvic parasympathetic nerves: arise at the sacral level of the spinal cord, excite the bladder, and relax the urethra
- Lumbar sympathetic nerves: inhibit the bladder body and excite the bladder base and urethra
- Pudendal nerves: excite the external urethral sphincter

These nerves contain afferent (sensory) as well as efferent motor axons.[5]

Parasympathetic Pathways

Parasympathetic preganglionic neurons innervating the lower urinary tract are located in the lateral part of the sacral intermediate gray matter in a region termed the sacral parasympathetic nucleus.[5] Parasympathetic preganglionic neurons send axons through the ventral roots to peripheral ganglia, where they release the excitatory transmitter acetylcholine (ACh). Parasympathetic postganglionic nerve terminals release ACh, which can excite various muscarinic receptors in bladder smooth muscles, leading to bladder contractions (Figure 1).

In humans, parasympathetic postganglionic neurons are located in the detrusor wall layer, as well as in the pelvic plexus. This is important in that patients with cauda equina or pelvic plexus injury, who are neurologically decentralized, may not be completely denervated. Cauda equina injury allows possible interconnection between afferent and efferent nerves at the level of the intramural ganglia.

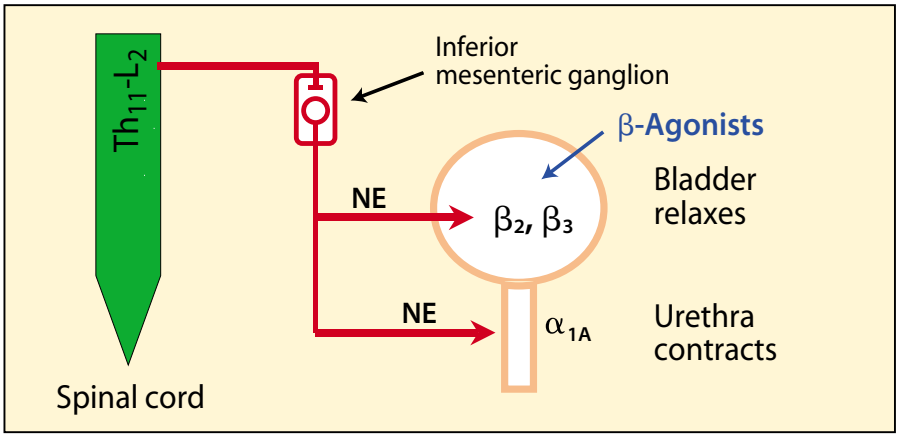
Sympathetic Pathways

Sympathetic outflow from the rostral lumbar spinal cord provides a noradrenergic excitatory and inhibitory input to the bladder and urethra.[6] The peripheral sympathetic pathways follow a complex route that passes through the sympathetic chain ganglia to the inferior mesenteric ganglia and then, via the hypogastric nerves, to the pelvic ganglia. Sympathetic preganglionic neurons synaptically connect with postganglionic neurons in the inferior mesenteric ganglion, as well as with postganglionic neurons in the paravertebral ganglia and pelvic ganglia. Ganglionic transmission in sympathetic pathways is also mediated by ACh acting on ganglionic-type nicotinic receptors. Sympathetic postganglionic terminals that release norepinephrine elicit contractions of bladder base and urethral smooth muscle and relaxation of the bladder body (Figure 2).

Somatic Pathways

Somatic efferent motoneurons that innervate the external striated urethral sphincter muscle and the pelvic floor

Figure 2. *Sympathetic (hypogastric nerve): Sympathetic postganglionic terminals that release norepinephrine (NE) elicit contractions of bladder base and urethral smooth muscle and relaxation of the bladder body.*



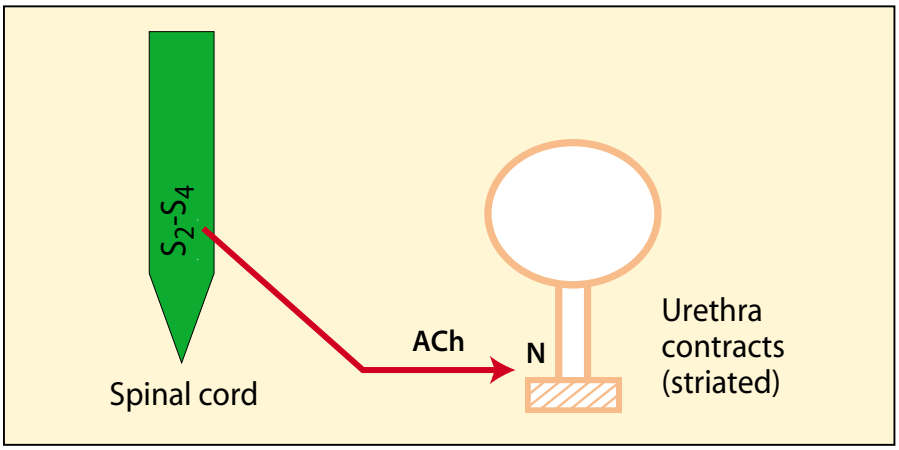


Figure 3. *Somatic (pudendal nerve): Somatic nerve terminals release acetylcholine (ACh), which acts on skeletal muscle–type nicotinic receptors (N) to induce a muscle contraction.*

musculature are located along the lateral border of the ventral horn in the sacral spinal cord, commonly referred to as Onuf's nucleus.[7] Sphincter motoneurons also exhibit transversely oriented dendritic bundles that project laterally into the lateral funiculus, dorsally into the intermediate gray matter, and dorsomedially toward the central canal. Somatic nerve terminals release ACh, which acts on skeletal muscle–type nicotinic receptors to induce a muscle contraction (Figure 3).

Afferent Pathways

The pelvic, hypogastric, and pudendal nerves contain afferent axons that transmit information from the lower urinary tract to the lumbosacral spinal cord.[2,5] The primary afferent neurons of the pelvic and pudendal nerves are contained in sacral dorsal root ganglia, whereas afferent innervation in the hypogastric nerves arises in the rostral lumbar dorsal root ganglia. The central axons of the dorsal root ganglion neurons carry sensory information from the lower urinary tract to second-order neurons in the spinal cord. Visceral afferent fibers of the pelvic and pudendal nerves enter the spinal cord and travel rostrocaudally within Lissauer's tract.

Pelvic nerve afferents, which monitor the volume of the bladder and the amplitude of bladder contractions, consist of small myelinated Aδ-fibers and unmyelinated C-fibers. Electrophysiologic studies in cats and rats have revealed that the normal micturition reflex is mediated by myelinated Aδ-fiber afferents that respond to bladder distension.[1]

Although sensing bladder volume is of particular relevance during urine storage, afferent discharges that occur during a bladder contraction have an important reflex function and appear to reinforce the central drive that maintains bladder contractions. Afferent nerves that respond to both distension and contraction, that is, "in-series tension receptors," have been identified in the pelvic and hypogastric nerves of cats and rats (Table 1).[8] Afferents that respond only to bladder filling have been identified in the rat bladder and appear to be volume receptors, possibly sensitive to stretch of the mucosa. In the cat bladder, some in-series tension receptors may also respond to bladder stretch. There is now evidence that many C-fiber bladder afferents in the rat are volume receptors that do not respond to bladder contractions, a property that distinguishes them from in-series tension receptors.[5]

Neuropharmacology

Cholinergic Mechanisms

Detrusor strips from healthy human bladders are contracted by cholinergic muscarinic receptor agonists and electrical stimulation of intrinsic cholinergic nerves. Contractile responses can be completely abolished by atropine.[1] There are at least 5 receptor subtypes based on molecular cloning and 4 different receptor subtypes based

Table 1
Bladder Afferent Neuron Properties

Afferent Fiber Type	Normal Function	Location	Inflammation Effect
C-fiber (unmyelinated axons)	Responds to stretch (volume sensors)	Mucosa	Increases discharge at lower threshold
	Nociception to overdistention	Mucosa	Sensitive to irritants
		Muscle	Becomes mechanosensitive and unmasks new afferent pathway during inflammation
Aδ-fiber (myelinated axons)	Senses fullness (wall tension)	Smooth muscle	Increases discharge at lower pressure threshold

on pharmacology (M_{1-5}). Pharmacologically, M_1, M_2, and M_3 receptor subtypes have been found in the human bladder by receptor binding assays.[9] Although ligand-receptor binding studies revealed that M_2 receptors predominate, M_3 receptors mediate cholinergic contractions.[10] Stimulation of M_3 receptors by ACh leads to phosphoinositol hydrolysis and, subsequently, to the release of intracellular Ca^{2+} and a smooth muscle contraction. It has been proposed that co-activation of M_2 receptors could enhance the response to M_3 stimulation through inhibition of adenylate cyclase and a subsequent suppression of sympathetically mediated depression of detrusor muscle, inactivation of K^+ channels, or activation of nonspecific cation channels.[5]

Activation of M_1 prejunctional receptors facilitates ACh release, whereas activation of M_2/M_4 receptors inhibits ACh release.

A study of mutant mice that lack the M_3 receptor gene demonstrated that this receptor subtype plays key roles in salivary secretion, pupillary constriction, and detrusor contraction.[10] However, M_3-mediated signals in digestive and reproductive organs are dispensable, likely because of redundant mechanisms through other muscarinic ACh receptor subtypes or other mediators. A study of M_2-receptor knockout mice has revealed that this receptor subtype plays a role in bladder contraction through inhibition of the relaxant effects induced by increased cyclic adenosine monophosphate (cAMP) levels in the bladder.[11]

It has also been documented that activation of M_1 prejunctional receptors facilitates ACh release,[12] whereas activation of M_2/M_4 receptors inhibits ACh release. It has been proposed that inhibitory M_2/M_4 receptors are preferentially activated by auto-feedback mechanisms during short periods of low-frequency nerve activity and, thereby, suppress cholinergic transmission during urine storage. M_1 receptors are activated during more prolonged, high-frequency nerve firing that occurs during voiding and, thus, participate in an amplification mechanism to promote complete bladder emptying.

The muscarinic receptor antagonists tolterodine and oxybutynin are the most widely prescribed therapies for urinary incontinence. Oxybutynin is a nonspecific muscarinic antagonist with additional smooth muscle relaxant properties.[1] These properties of smooth muscle relaxation may be clinically relevant only when the drug is administered as an intravesical instillation. Because new antimuscarinic drugs are a "hot topic" for pharmaceutical development, urologists should be aware of the muscarinic receptor subtypes and their distribution in the lower urinary tract and other organs.

An additional issue regarding the effects of antimuscarinic drugs is clinical relevancy. Antimuscarinic drugs are metabolized, and their metabolites have pharmacologic effects. For example, oxybutynin has less of a dry-mouth effect than does its metabolite N-desethyloxybutynin.[13] Therefore, the controlled-release formulation of oxybutynin maintains the efficacy of immediate-release oxybutynin but with significantly fewer side effects. Transdermal delivery of oxybutynin results in a lower concentration of metabolite and an improved side effect profile compared with the oral formulation.[5]

Muscarinic Selectivity

Pharmacologically defined receptor subtype–selective drugs have been developed. Darifenacin and vamicamide have recently been demonstrated to be selective for the M_3 receptor subtype.[10] However, they are not necessarily tissue-selective, as salivary glands and other tissues also contain M_3 muscarinic receptors. Several drugs are currently being tested for their tissue selectivity. In a cat model, tolterodine appears to have selectivity for the bladder over the salivary gland, although it may not be M_3 subtype–selective.[14] Therapeutically, however, it is more important for a drug to be tissue-selective than subtype-selective.[1] A truly bladder-selective antimuscarinic drug that causes no dry mouth is the ultimate goal for overactive bladder drug therapy.

Purinergic Mechanisms

Purinergic contribution to parasympathetic stimulation in vivo, or field stimulation in vitro, has been demonstrated in a variety of species, including rat, rabbit, and guinea pig. Pharmacologic and molecular studies have shown $P2X_1$ to be the predominant purinoceptor subtype in bladder smooth muscle to induce its contraction.[15] Although there is less evidence that purinergic neurotransmission exists in man, at least in regard to normal responses to stimulation, an increase in purinergic function may contribute to the unstable bladder under pathologic conditions such as bladder outlet obstruction.

Adrenergic Mechanisms

α-Adrenergic. Although α-adrenergic stimulation is not prominent in the healthy bladder, recent evidence indicates that, under pathologic conditions, α-adrenergic receptor density can increase to such an extent that the norepinephrine-induced response

in the bladder is converted from relaxation to contraction. It has been hypothesized that this shift in response may contribute to the bladder hyperactivity observed in a variety of pathologic conditions, including obstructive uropathy and incontinence. Lepor and colleagues[16] compared receptor densities in normal and hyperreflexic human bladders and demonstrated significantly lower muscarinic receptor densities and higher α-adrenoceptor densities in the hyperreflexic bladders.

ß-Adrenergic. The bladder smooth muscle contains 2 subtypes of ß-adrenoceptors ($ß_1$- and $ß_2$-receptors). Although $ß_2$-adrenoceptors have an important role in muscle relaxation via activation of adenylate cyclase, recent evidence indicates that the $ß_3$-receptor subtype mediates relaxation of human detrusor muscles, with predominant expression of $ß_3$-adrenoceptor messenger RNA in human bladder tissue.[17,18]

ß-Adrenergic–stimulated relaxation is mediated through the stimulation of adenyl cyclase and the accumulation of cAMP. Thus, it is suggested that activation of bladder $ß_3$-adrenoceptors could be an effective treatment of bladder overactivity.[17] ß-Adrenergic blockers have also been advocated for urinary incontinence due to inappropriate reflex urethral relaxation, because propranolol prevents the reduction in urethral pressure following sacral root stimulation. However, $ß_2$-adrenergic antagonists are not particularly useful in treating bladder or urethral disorders.

Nitric Oxide

Nitric oxide (NO), which has been implicated as an important neurotransmitter in urethral relaxation and penile erection, is also involved in controlling bladder afferent nerve activity. Inhibitors of nitric oxide synthase (NOS), administered systemically or intrathecally, do not affect normal micturition in conscious or anesthetized rats. However, bladder hyperreflexia induced by irritation with turpentine or acetic acid is ameliorated by spinal application of NOS inhibitors.[19] Intravesically administered capsaicin induces bladder hyperactivity that is not influenced by NOS inhibitors, although the behavioral effects of the irritation are reduced. The inhibitory components of the somatovesical reflex elicited by electrical stimulation of the tibial nerve are reduced with NOS inhibition. Intravesical application of NO can also suppress bladder hyperactivity caused by cyclophosphamide-induced bladder irritation in rats. These effects are mediated by suppression of Ca^{2+} channel activity in bladder afferent pathways.[20]

Tachykinins

The tachykinins are a family of small peptides, the main members of which are substance P, neurokinin A, and neurokinin B. Tachykinins are found in both central and peripheral nervous systems. In the peripheral nerves, substance P and neurokinin A are predominately located in the terminals of nonmyelinated, sensory C-fibers.[21] The diverse biologic effects of the tachykinins are mediated via 3 receptors—NK1, NK2, and NK3—belonging to a superfamily of 7 transmembrane-spanning G-protein–coupled receptors. Studies, including the most recent report by Ruggieri and colleagues,[22] support the presence of NK1 and NK2 receptors, but not NK3 receptors, in the guinea pig bladder. NK1- and NK2-specific antagonists were demonstrated to reduce the painful behavioral response in an experimental bladder inflammatory cystitis model. Study results suggest that tachykinin release from capsaicin-sensitive sensory C-fibers in response to irritation is mediated primarily by NK2 receptors and partially by NK1 receptors.

Capsaicin, Resiniferatoxin, Vanilloid Receptor, and C-Fiber Pharmacotherapy

Capsaicin and its ultrapotent analogue resiniferatoxin are vanilloids that stimulate and desensitize a specific population of sensory nerves (predominantly unmyelinated C-fibers) that transmit pain signals and release neuropeptides. Because of their unique property of C-fiber desensitization, the vanilloids are undergoing intensive study as a therapy for pain not only in the bladder but also in other systems.[23]

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The normal sensations of bladder filling appear to be mediated by small myelinated fibers (Figure 4). In the cat, Aδ-fibers have pressure thresholds in the range of those at which humans report the first sensation of bladder filling. Conversely, C-fiber afferents, which are small and unmyelinated, have high mechanical thresholds and do not respond to even high levels of intravesical pressure in the cat. However, C-fiber afferents are activated by noxious chemical irritation or by cold (Figure 5). Furthermore, in the irritated state, these fibers become responsive to low-pressure bladder distension, similar to mechanoreceptive Aδ-fibers. C-fibers, therefore, are normally "silent" and appear to have the specific function of signaling inflammatory

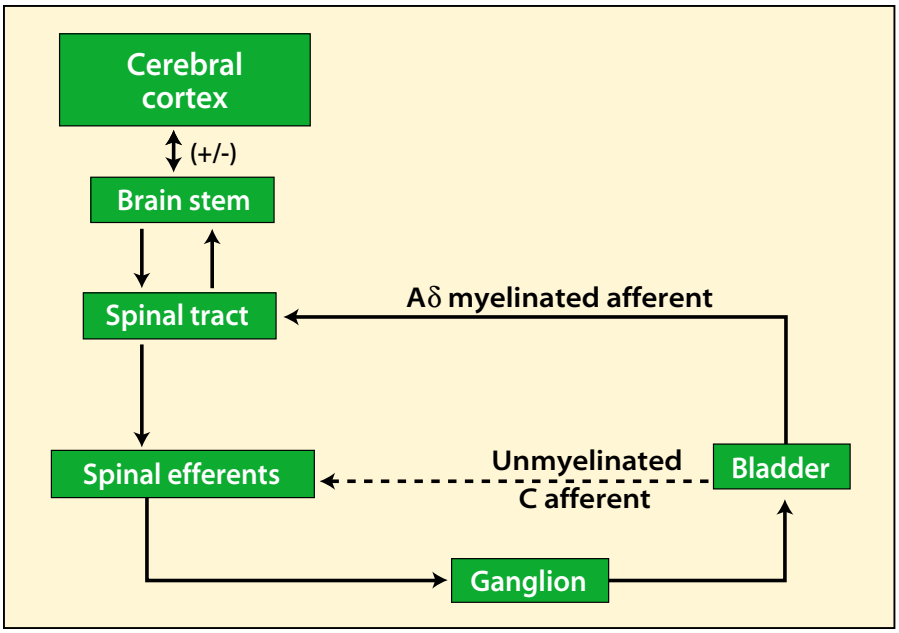

Figure 4. *Normal control of micturition: The normal sensations of bladder filling appear to be mediated by small myelinated fibers.*

or noxious events in the bladder.[23]

The vanilloids capsaicin and resiniferatoxin activate nociceptive sensory nerve fibers through a recently discovered ion channel known as vanilloid receptor subtype 1 (TRPV1).[24] This receptor, a nonselective cation channel, is activated by increases in temperature to within the noxious range and by protons, suggesting that it functions as a transducer of painful thermal stimuli and acidity in vivo. When TRPV1 is activated, the channel opens, allowing an influx of calcium and sodium ions that depolarizes the nociceptive afferent terminals, which initiates a nerve impulse that travels through the dorsal root ganglion into the central nervous system (CNS). Noxious temperature uses the same elements, which explains why the mouth feels hot when eating chili peppers.

Euphorbium is a drug derived from the air-dried latex (resin) of the cactus-like plant *Euphorbia resinifera*. *E resinifera* belongs to the Euphorbiaceae family, commonly known as the spurge family, one of the most important families of medicinal plants.[23] In 1975, the principal active ingredient in Euphorbium was isolated and named resiniferatoxin (RTX). RTX was recognized as an ultrapotent analogue of capsaicin; however, it has unique pharmacologic effects as well, such as desensitization without prior excitation of the pulmonary chemoreflex pathway. RTX is now in Food and Drug Administration phase 2 trials for the treatment of interstitial cystitis.

Serotonergic Mechanisms

In the CNS, serotonin-containing neurons in the raphe nucleus of the caudal brain stem send projections to the dorsal horn, as well as to the autonomic and sphincter motor nuclei in the lumbosacral spinal cord. In cats, activation of raphe neurons or serotonin receptors in the spinal cord inhibits reflex bladder contractions and firing of the sacral efferent pathways to the bladder, as well as firing of spinal dorsal horn neurons elicited by stimulation of pelvic nerve afferents. In a bladder-irritation model, duloxetine, a combined noradrenaline and serotonin reuptake inhibitor, has been shown

Figure 5. *Altered neurocontrol in overactive bladder and interstitial cystitis: C-fibers, which are normally "silent," appear to have the specific function of signaling inflammatory or noxious events in the bladder.*

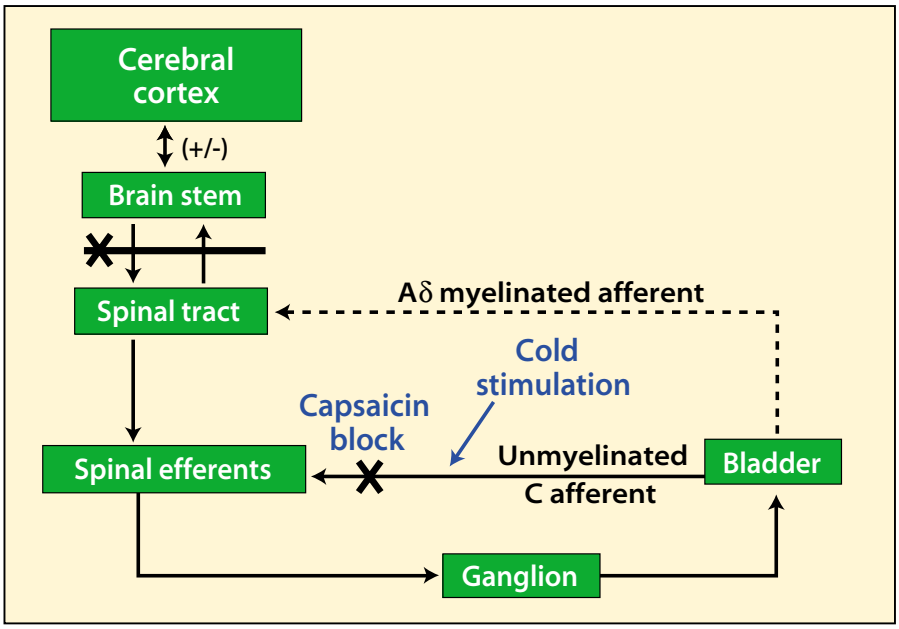

Table 2
Promising Targets to Treat Overactive Bladder

- Purine: An increase in purinergic function may contribute to the unstable bladder. Purinergic antagonists may be a promising avenue of therapy.
- ß-Adrenergic: Activation of bladder $ß_3$-adrenoceptors may be an effective treatment of bladder overactivity.
- Nitric oxide: Intravesical application of nitric oxide donor can suppress bladder hyperactivity.
- Tachykinins: Tachykinin release from capsaicin-sensitive sensory C-fibers in response to irritation is mediated primarily by NK1 and NK2 receptors and may be reversed by tachykinin antagonists.
- Vanilloids: Intravesical resiniferatoxin is currently being studied in FDA phase 2 trials for the treatment of interstitial cystitis.

FDA, Food and Drug Administration.

to increase neural activity of both the urethral sphincter and the bladder. Duloxetine appears to have due effect on both the bladder and the sphincter and has been proposed as a treatment of both stress and urge incontinence.[25,26] Duloxetine increases neural activity to the external urethral sphincter and decreases bladder activity through effects on the CNS.[27] This drug is currently being studied in clinical trials, and results are eagerly awaited.

Mechanisms of Bladder Overactivity

A variety of models have been used to explore the pathogenesis of detrusor overactivity and formulate therapies for urge incontinence. Models for bladder overactivity in several species have been developed relevant to spinal cord injury, obstruction, denervation, Parkinson disease, interstitial cystitis, diabetes, multiple sclerosis, and aging.[5] More recently, the spontaneously hypertensive rat has provided a useful genetic model for bladder overactivity.[28]

A common feature of many of these models is that changes in smooth muscle function can elicit long-term changes in nerves. Investigators are accustomed to examining short-term effects; however, there is now a greater appreciation that long-term events involving growth factors lead to plasticity in neural pathways, with implications for disorders of micturition. Neurotransmitters, prostaglandins, and neurotrophic factors, such as nerve growth factor, provide mechanisms for communication between muscle and nerve. Disturbances in these mechanisms can cause bladder overactivity due to alterations in autonomic reflex pathways. This bladder overactivity can, in turn, lead to urge incontinence.

Cystometry and urinary frequency, which are commonly used to define bladder overactivity, can be used to monitor response to drugs or other therapies. A multidisciplinary approach to treatment, incorporating biochemical, molecular, pharmacologic, physiologic, and behavioral

Main Points

- The process of micturition is controlled by neural circuits in the brain and spinal cord coordinating the activity of smooth muscle in the bladder and urethra. Because this process is complex, a variety of neurologic disorders and injuries can result in urge incontinence.
- The lower urinary tract is innervated by 3 sets of peripheral nerves: pelvic parasympathetic nerves, which arise at the sacral level of the spinal cord, excite the bladder, and relax the urethra; lumbar sympathetic nerves, which inhibit the bladder body and excite the bladder base and urethra; and pudendal nerves, which excite the external urethral sphincter.
- Detrusor strips from healthy human bladders are contracted by cholinergic muscarinic receptor agonists and electrical stimulation of intrinsic cholinergic nerves. Pharmacologically, M_1, M_2, and M_3 receptor subtypes have been found in the human bladder by receptor binding assays.
- Oxybutynin is a nonspecific muscarinic antagonist with additional smooth muscle relaxant properties. Transdermal delivery of this agent results in a lower concentration of its metabolite, N-desethyloxybutynin, and an improved side effect profile compared with the oral formulation.
- Advances in the field of neurourology have increased our understanding of neural control of the lower urinary tract and the etiology of voiding dysfunction. In addition to traditional drugs, which target the smooth muscle or postjunctional muscarinic and adrenergic receptors, it is now clear that targets at other sites, such as afferent neurons, efferent nerve terminals, urothelial cells, and the central nervous system, are equally important for drug development.

methods, can provide insight into the pathogenesis of bladder overactivity.

Conclusion

Diseases of the nervous system in adults can disrupt the voluntary control of micturition and cause the reemergence of reflex micturition, resulting in bladder hyperactivity and incontinence. During the past several years, research in the field of neurourology has led to the emergence of new concepts regarding the neural control of the lower urinary tract and the etiology of voiding dysfunction. Thus, in addition to traditional drugs, which target the smooth muscle or postjunctional muscarinic and adrenergic receptors, it is now clear that targets at other sites, such as afferent neurons, efferent nerve terminals, urothelial cells, and the CNS, are equally important for drug development (Table 2).

Because of the complexity of the central and peripheral nervous control of the lower urinary tract, which utilizes a wide variety of neurotransmitters, it is probable that numerous classes of drugs will eventually be used to treat voiding problems. An understanding of the physiologic events that mediate micturition and continence provides a rational basis for the management of lower urinary tract dysfunction. ■

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